REMARKS

Applicants submit herewith a Notice of Appeal of U.S. application Serial No. 09/600,766, filed on July 21, 2000.

Claims 1, 4-11, and 13-20 are pending in the instant application. Claims 2, 3, and 12 were previously cancelled, without prejudice. Claims 1 and 10 have been amended. Accordingly, claims 1, 4-11, and 13-20 will be pending in the application upon entry of the instant Amendment.

Support for the amendment to claims 1 and 10 can be found throughout the specification and clams as originally filed. In particular, support for the amendments to claims 1 and 10 may be found, at least at, page 3, lines 17-31 of the specification. No new matter has been added.

Cancellation of and/or amendments to the claims as originally filed should in no way be construed as an acquiescence to any of the rejections/objections set forth in the instant Office Action, and were made solely to expedite prosecution of the above-identified application. Applicants reserve the right to pursue the claims as originally filed, or similar claims, in one or more patent applications.

Rejection of Claims 1, 4, 10-11, and 13-14 Under 35 U.S.C. § 102(a)

The Examiner has rejected claims 1, 4, 10-11, and 13-14 under 35 U.S.C. § 102(a) as being anticipated by Takada *et al.* According to the Examiner, Takada *et al.* allegedly teaches viral carriers comprising an Ebola glycoprotein expressed on the surface of the carrier and use of said carrier to target a gene to a host cell.

Applicants traverse the foregoing rejection and submit that Takada *et al.* does not teach or suggest the now pending claims. In particular, Takada *et al.* does not teach or suggest a genetic construct comprising a gene operatively-linked to a carrier, wherein the carrier is associated with an Ebola transmembrane form of viral glycoprotein or derivative thereof, which is expressed on the

surface of the carrier, wherein the viral glycoprotein or the derivative thereof retains the capability of targeting cell types which are naturally infected with Ebola virus.

The VSV-Reston GP virus taught in Takada *et al.* is a recombinant virus, not a vector as claimed by the present invention. Therefore, the assays taught in Takada *et al.* only measure viral replication and do not quantitate the efficacy of gene delivery. Takada *et al.* does not teach or suggest the use of the VSV-Reston GP virus for delivery of a recombinant gene to modify cellular gene expression in a specific and functional manner. In addition, Takada *et al.* does not teach or suggest differential targeting of the Ebola GP to specific cell types, as claimed by the present invention. Furthermore, Takada *et al.* does not provide any evidence that Ebola pseudotyping could be applied to vectors for gene delivery or that it might be applied to anything other than a close relative, *e.g.*, VSV.

Moreover, Takada *et al.* reports incorporation of one viral glycoprotein gene, Ebola Reston, into another virus closely related to it. Ebola virus is a negative strand filamentous RNA virus most closely related to the paramyxovirus. Thus, while Takada *et al.* discloses an exchange between two very similar viruses, Takada *et al.* does not teach, suggest, or apply these findings to viruses which are fundamentally different in structure, such as a retroviral or lentiviral vector, as claimed by the present invention.

In view of the foregoing, Applicant respectfully submits that the pending claims are not taught or suggested by Takada *et al.* Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

Rejection of Claims 1, 5, 8, 10-11, and 13-14 Under 35 U.S.C. § 102 (e)

The Examiner rejected claims 1, 5, 8, 10-11, and 13-14 under 35 U.S.C. § 102 (e) as being anticipated by Schreier *et al.*

Applicants traverse the foregoing rejection and submit that Schreier *et al.* does not teach or suggest the pending claims. In particular, Schreier *et al.* does not teach or suggest a genetic construct comprising a gene operatively-linked to a carrier, wherein the carrier is associated with an Ebola transmembrane form of viral glycoprotein or derivative thereof, which is expressed on the

surface of the carrier, wherein the viral glycoprotein or the derivative thereof retains the capability of targeting cell types which are naturally infected with Ebola virus.

Schreier *et al.* discloses a synthetic viral lipid vesicle having a unilamellar membrane with an outer surface and a stable, rigid structure, and a protein inserted into the outer surface of the membrane. Schreier *et al.* provides a laundry list of human viruses, including the Ebola virus, which can be used in connection with the novel lipid vesicles of the invention. However, the teachings of Schreier *et al.* are limited to a synthetic lipid vesicle, wherein a protein is inserted into the outer surface of the membrane. In contrast, the present invention teaches that the genetic constructs of the invention comprise a gene to be transferred operatively-linked to an appropriate transfer vehicle or carrier, wherein the transfer vehicle or carrier is associated with a transmembrane form of viral glycoprotein, which retains the capability of targeting cell types which are naturally infected with Ebola virus. The present invention is thus further distinguishable from the teachings of Schreier *et al.*, because according to the instant invention, the gene to be transferred will be targeted to cell types naturally infected with Ebola virus including, without limitation, endothelial cells, hepatocytes, monocytes and related cell types such as dendritic cells (page 2, lines 3-5 of the specification).

In view of the foregoing, Applicant respectfully submits that the pending claims are not anticipated by Schreier *et al.* Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejection of Claims 10-11 and 13-20 Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 10-11 and 13-20 under 35 U.S.C. § 112, first paragraph as "containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." According to the Examiner, the claims are not enabled because of the quantity of experimentation required to perform the claimed methods and the unpredictability in the art of gene therapy. In particular, the Examiner indicates that "at the time of filing of the instant invention, no successful examples of gene therapy or immunization in humans using recombinant vectors expressing heterologous antigens had been unambiguously demonstrated."

Applicants respectfully traverse this rejection. Applicants point out that the specification provides ample guidance to enable one of ordinary skill in the art to make and use the invention.

The instant invention is directed to methods of targeting a gene to a cell by administering to a cell population a genetic construct comprising the gene operatively-linked to a carrier, wherein the carrier is associated with an Ebola transmembrane form of viral glycoprotein or derivative thereof, which is expressed on the surface of the carrier, wherein the viral glycoprotein or the derivative thereof retains the capability of targeting cell types which are naturally infected with Ebola virus.

It is Applicant's position that, given the guidance in the specification and the teachings in the art at the time the invention was made, one of ordinary skill in the art would be able to practice the invention as claimed using no more than routine experimentation. In support of this position, Applicants point to *In re Wands,* 858 F.2d 731; 8 U.S.P.Q.2D (BNA) 1400, (CAFC 1988). In that case the Court held that a reasonable amount of experimentation is permitted to practice a claimed invention. The Court stated that "the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed."

In the instant Office Action, the Examiner cites a case in which gene therapy was used to cure X-linked combined immunodeficiency (X-SCID). The Examiner asserts that "the vectors themselves may have caused leukemia." In response, Applicants submit that the future of gene therapy is often debated and there are numerous publications both in support of gene therapy as a viable treatment as well those which cast doubt on the feasibility of gene therapy, such as that cited by the Examiner. Applicants respectfully submit that the scope of the invention should not be limited by the potential difficulties involved in gene therapy generally, nor by the Examiner's general anticipated failure of the procedure. The scope of the invention should be reviewed according to the specifically claimed subject matter and the support for that subject matter contained in the specification.

Moreover, the study to which the Examiner refers demonstrated that gene therapy as a technique worked. In particular, the Marshall article cited by the Examiner indicates that the X-

SCID cure "is credited as the first unequivocal success for gene therapy." Indeed, in this particular case, use of gene therapy cured the disease it was meant to cure. However, there was an unintended consequence wherein the retrovirus inserted itself into a gene that is known to promote cancer. The FDA's Biological Response Modifiers Advisory Committee later met on February 28, 2003 to discuss the policy implications of gene therapy. At this meeting, the Committee voted 18 to 1 in favor of removing the holding on retroviral gene therapy trials in hematopoietic stem cells on a case-by-case review, a summary of which is attached hereto as Appendix A.

Applicants submit that the specification discloses ample guidance for one of skill in the art to make and use the genetic constructs and methods of the claimed invention. Specifically, Applicants submit that the instant specification teaches methods for determining, for example, the specificity of Ebola virus glycoproteins (Example 1) and the efficacy of targeting cells with gene transfer vectors (Example 2). Furthermore, the instant application teaches that the methods of the present invention comprise administering to an *in vivo* cell population a construct of the present invention. Administration can be by any of the routes normally used for *in vivo* gene therapy, known to the skilled artisan, such as direct delivery to cells via a gene gun, and other known techniques. Thus, Applicants respectfully submit that while aspects of the field of gene therapy may not be an exact science, the genetic constructs and methods taught by Applicants are sufficiently described to enable an ordinary skilled artisan to make and use the claimed invention using only routine experimentation.

Based on the foregoing, Applicants respectfully submit that pending claims fulfill the 35 U.S.C. §112, first paragraph requirements. Applicants therefore respectfully request reconsideration and withdrawal of this rejection.

Rejection of Claims 1, 4-11, and 13-20 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 1, 4-11, and 13-20 under 35 U.S.C. § 112, second paragraph as "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." The Office Action further asserts that "[c]laims 1 and 10-12 (and dependent claims) are vague in the recitation of the phrase 'viral

glycoprotein or derivative thereof' because it is unclear what the term 'derivative thereof' encompasses."

Applicants traverse the foregoing rejection and submit that the pending claims distinctly claim the subject matter which Applicants regard as their invention. As set forth in the Amendment filed on February 3, 2003, the instant specification discloses that "derivatives of the transmembrane glycoprotein which retain the capability of targeting specific cell types, may also be employed, for example, the transmembrane glycoproteins may be mutated, *e.g.*, toxic regions may be removed to improve producer cell viability (see Figure 10)" (see page 3, lines 28-31 of the specification). Furthermore, the instant specification provides a summary of the characterization of glycoprotein and glycoprotein derivatives for their ability to pseudotype to induce cytotoxicity in producer cells, as set forth in Figure 10. However, in the interest of expediting prosecution, and in no way conceding to the validity of the Examiner's rejection, Applicants have amended claims 1 and 10 as suggested by the Examiner. In particular, claims 1 and 10, as amended herein, recite that the derivatives of the Ebola transmembrane glycoprotein retains the capability of targeting specific cell types which are naturally infected with Ebola virus. Applicants thus respectfully request that the Examiner withdraw this rejection.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 12-0080, under Order No. UMV-1474US from which the undersigned is authorized to draw.

Dated: November 3, 2003

Respectfully submitted,

By _____

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